REMARKS

Reconsideration is requested.

Claims 1-4, 6-9, 11, 12, 31, 34, 37-39 and 44-54 are pending. Claims 1-4, 6-9, 11 and 12 have been withdrawn from consideration. Claim 34 has been amended, without prejudice. Claims 51-54 have been added. Support for the additional claims may be found, for example, in claim 34, and in the specification at page 44, lines 13-18, page 46, lines 30-32, and page 47, lines 1-7. No new matter has been added.

The Examiner is again requested to return initialed copies of the PTO-1449 Forms, filed with the Information Disclosure Statements of November 15 and December 16, 2005, to the undersigned. A previous similar request was filed July 3, 2008.

The Examiner is also requested to confirm receipt of the priority document from the International Bureau as indicated in the Notice of Acceptance dated October 10, 2006. Similar requests were filed on September 13, 2007 and January 23, 2008 and July 3, 2008.

The Examiner is requested to have a BIB DATA SHEET prepared and place in the PTO IFW for the above which confirms that the requirement for claiming priority have been met.

The Section 112, second paragraph, rejection of claim 34 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments and the attached.

Claim 34 has been revised, without prejudice, to delete the objected-to phrase "chemically protected form" to advance prosecution by narrowing the outstanding issues.

The Examiner has asserted that the term "solvate" and the phrase "C_{5-6} arylene" are allegedly indefinite.

The Examiner has not commented on or refuted the applicants previous evidence that the term "solvate" is well understood by one of ordinary skill in the art and accepted as a definite term in claims of issued U.S. patents. See Remarks of the Amendment After Final Rejection dated March 20, 2008. The previously submitted results of the U.S. Patent Office search is evidence that the rejected recitation is well understood by those of ordinary skill in the art. The Examiner has at least not repeated the previous assertion that "What is allowed in the issued US patent data base is of no consequence to prosecution at hand." See page 3 of the Office Action dated December 21, 2007. The terms and phrases of allowed U.S. patents in the chemical arts evidence a recognized understanding in the art by those of ordinary skill in the art, including patent applicants, scientists, engineers and Patent Examiners.

Moreover, attached is a copy of a Decision of the Board of Appeals and Interferences in Ex parte Joachim Gante, Appeal No. 2006-0600, May 6, 2002, wherein the Board has recognized that the scope of "solvates" as recited in the claims at issue was known. The Board reversed the Examiner's Section 112, second paragraph, rejection of the claims based on the recitation of "solvates".

Specifically, the Gante Board summarized the issue as follows:

> According to the examiner (Answer, page 3) the "[s]cope of 'solvates' as recited in ... [the] claims is unknown." The examiner finds (id.) "[g]enerally not all solvents can form solvates with all compounds ... [and] it is not routine for any and every type of solvent for form solvate(s) with specific compounds." According to the examiner (Answer, page 4)

> "[i]n the absence of any guidance in the specification ... or in any relevant prior art,[ ]one cannot readily determine what is and what is not within the instant scope of solvates." See page 8 of the attached Decision.

In reversing the Examiner, the Gante Board agreed with the following arguments from the appellants:

> In response, appellants argue (Brief, page 3) "[t]hat all solvents cannot form solvates with all compounds is not seen to be relevant herein. The relevant inquiry is whether it would be known to one of ordinary skill in the art what solvents form physiologically acceptable solvates with the compounds of formula I." In this regard, appellants argue (Brief, page 4), with reference to Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986), "the selection of useful solvents and formation of solvates is highly routine in this art. Appellants need not provide in their specification a description of matter which is common and routine in the art. A 'patent need not teach, and preferably omits, what is well known in the art.'" According to appellants' (Reply Brief, page 2) "[b]ecause selection of the appropriate solvents for forming solvates was routine to one of ordinary skill in the art, the metes and bounds of the term were reasonably determinable using only ordinary skill in the art." We agree. See pages 8-9 of the attached Decision.

As the present Examiner is believed to have rejected claim 34 as allegedly being indefinite for reasons similar to those found unpersuasive by the Gante Board, the present Examiner is requested to withdraw the Section 112, second paragraph, rejection of claim 34 based on the recitation of "solvate".

As for the recitation of "C_{5-6} arylene" in claim 34, the applicants refer the Examiner to, for example, the description at page 12, wherein C_{5-6} arylene refers to both carboarylene and heteroarylene groups having five or six ring atoms. Thus, a C_5 arylene structure would include diradicals of, for example, pyrrole, furan and thiophene (see

page 12, lines 26-28 along with page 10, lines 16-30). The term "C_{5-6} arylene" is therefore clear to those of skill in the art.

Withdrawal of the Section 112, second paragraph, rejection of claim 34 is requested.

The Section 112, first paragraph "enablement", rejection of claims 31, 34, 37-39 and 44-48 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following and the attached.

The applicants believe that the Examiner's rejection is based on unsupported conclusions. The Examiner has not presented documentation or evidence that specifically relates to the types of compounds that are presently claimed. The Examiner has only provided general arguments as to the alleged unpredictability of organic synthesis and biological chemistry in general.

The Examiner has rejected the claims on the basis that there is allegedly no teaching in the application that would allegedly allow the compounds of the invention to be prepared across the full scope of the claims. The Examiner also rejected the claims on the basis that the biological activity of all the compounds claimed cannot, allegedly, be extrapolated from the examples in the application.

Preparation of the Claimed Compounds

Table 4 of the application provides evidence that compounds having a high structural similarity to the claimed compounds may be readily obtained from commercial sources. One of ordinary skill in the art will appreciate this to be indicative of the fact that such structures are accessible without undue burden.

By inference, the ordinarily skilled person will appreciate that the compounds of the invention could be obtained in methods similar to those known to the ordinarily skilled person for the preparation the compounds in Table 4. In particular, Table 4 includes aryl compounds having a range of thiol substituents. These thiol substituents correspond closely to the group -S-L^1-COO-R^6 in the present claims.

The application also provides examples of methods for the preparation of compounds having a central pyridine core (see, for example, page 38 onwards). The discussion of the synthesis of these compounds provide guidance as to the type of transformations that are possible and predictable on a core structure which is highly similarity to the claimed compounds.

The Examples in the application also provide direction to the ordinarily skilled person in the synthesis of compounds having a range of R^3 and L^9 groups. The step of introducing this diversity may include the reaction of a protected hydroxylamine with an appropriate carboxylic acid (or activated acid) bearing the R^3 and L^9 groups. This step is described on page 53, with respect of compound viii, an intermediate in the synthesis of compound ix.

The Examiner notes that the application provides exemplification for hydroxylamide formation at a benzylic position. The applicants submit that this teaching can be extended to the formation of other hydroxylamide forms. The transformation of a hydroxy group to a hydroxylamine group can be followed by coupling to an appropriate amide. The Examiner has not provided evidence that the art is unreasonably unpredictable in this regard.

Functional group transformations, such as those that form hydroxylamines are well known in the art. Some of these are discussed in, for example, March's *Advanced Organic Chemistry* (3rd Edition, Wiley-Interscience, New York, 1985), a text that is familiar to most chemists of ordinary skill. One entry in this textbook refers to the preparation of hydroxylamines from aryl and aliphatic nitro compounds (see Reaction 9-50, page 1104, copy attached). Hence, even if the displacement reaction referred to by the Examiner is "unavailable for making L4-arylene variable" (see page 6 of the Office Action dated May 1, 2008), which is not admitted, the art clearly indicates that other approaches to hydroxylamines are possible. From the hydroxylamine it is possible to access the hydroxylamide, using an appropriate protecting group strategy if necessary (as described in the present application and also by reference to Greene and Wuts *Protective Groups in Organic Synthesis*). The hydroxylamine may therefore be used to access compounds where L4 comprises a hydroxylamide linked to either an arylene or akylene group.

The Examiner's discussion on methods for the preparation of compounds within the scope of the claims is therefore unfounded given the availability of compounds of very similar structure within the art. As noted above, the Examiner has not provided any specific support for the Examiner's assertions regarding compound reactivity. The Examiner has provided no citation that would suggest that the compounds of the invention, or compounds having high structural similarity to those compounds of the invention, are not accessible using the range of chemistries known to the ordinarily skilled person.

The applicants should not be required to provide explicit direction or guidance for procuring all the starting materials required for the compounds encompassed by the present claims, as appears to be alleged by the Examiner. Such starting materials are believed to be well known and readily obtainable to those of ordinary skill in the art. For example, the mercapto compound used in the preparation of compounds A and E is available from commercial sources (see the Aldrich catalogue, for example, CAS number 4521-31-7).

The Examiner is not believed to have established a *prima facie* case of a lack of enabling support in the specification. The Examiner is not believed to have demonstrated that compounds within the scope of the claims cannot be prepared with reasonable experimentation.

Biological Activity of the Claimed Compounds

The claimed compounds are similar and based on a highly conserved core comprising a central benzene ring that is 1,4-disusbtituted. For each of the claimed compounds, one of the ring substituents is a group comprising a hydroxylamide. The other ring substituent is a thioether that is linked to an optionally functionalised carboxyl group.

The Examiner notes that a hydroxylamide group must be present "some where" (see page 6 of the Office Action dated May 1, 2008) in the compound of the invention. The present claims clearly define the location of this group to a specific site within the compound structure: the hydroxylamide is a component of L^4 which is a substituent at a particular site on the benzene ring. Within L^4, the hydroxylamide may be flanked by a

very limited number of groups (C_{1-4}alkylene, C_{5-6}arylene and C_{1-4}alkylene-C_{5-6}arylene) or not at all. Thus, it is maintained that the location of the hydroxylamide group within the claimed compound structure is not an "extremely broad generalization" as asserted by the Examiner. Id. This group is located specifically in the present claims and hence one of ordinary skill in the art would not believe that the scope of the claimed compounds is in "contradiction with the basis of quantitative structure-activity relationship", as asserted by the Examiner. Id.

The application also provides evidence that compounds having a hydroxylamide group at this location are capable of inhibiting the growth of HL60 cells and/or inhibiting glyoxylase I (see page 54, lines 24 onwards).

The preparation of four compounds is described in the application, and each of those compounds is shown to have biological activity, either in a HL60 cell growth inhibition assay, a glyoxylase I inhibition assay or both. Each of the compounds prepared is capable of exerting a quantifiable biological effect.

The biological data recorded in the glyoxylase I inhibition assay of the specification demonstrates that both compounds exhibit good glyoxylase I inhibition, and the IC50 values are well within an order of magnitude difference.

Where there are differences between the biological effects of the compounds, the applicants have provided an explanation, while one is not necessarily believed to be required. Thus, compounds iv and ix show relatively low percentage inhibition of glyoxylase I activity. However, as the applicants suggest in relation to the cell assay, it

is believed that these compounds are converted to the acid form in the cell culture, and are thereby able to exert a biological effect.

The lack of data for compound A in the HL60 cell assay in the application is a result of the compound not having been tested. This compound was nevertheless active in the glyoxylase I inhibition assay (see example 5).

As noted above, the compounds of the invention share a common core with a conserved substitution pattern. The compounds of the invention have a range of different substituents on the central core. However, these substituents are specifically defined: one substituent comprises a hydroxylamide group at a specified location, whilst the other substituent is a thioether linked to an optionally derivatised carboxylic acid. Given the structural similarity between members of the claimed group, the ordinarily skilled person would reasonably have predicted that the members of that group would be active in a HL60 cell growth inhibition assay, a glyoxylase I inhibition assay or both. On the basis of the application as filed, and the common general knowledge, the ordinarily skilled person would not have been presented with undue experimentation to identify compounds within the scope of the present claims having biological activity.

Solvates

The Examiner further asserts the claims are allegedly not supported by an enabling disclosure due to the recitation of solvates. A similar issue was discussed by the Board in the attached and above-discussed Ex parte Joachim Gante wherein the Board reversed the Examiner.

Initially, the applicants note that claims are not lacking in enabling support where one would require only routine experimentation to make and use the claimed invention.

The applicants submit that one of ordinary skill will be able to make solvates of the claimed compounds from the teachings of the specification as well as the generally advanced level of skill in the art.

A patent specification is required to teach one of ordinary skill in the art how to make and use the claimed invention without undue experimentation. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test for whether experimentation would be undue is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine. Id. at 1404.

The issue in In re Wands was whether the applicant had enabled one of ordinary skill in the art to make high-affinity IgM antibodies against HbsAg that were needed to practice the claimed invention. Id. at 1402. The Examiner in Wands had rejected the claims as allegedly not being enabled by the specification due to the alleged unpredictability and unreliability of the production of high-affinity IgM anti-HBsAg antibodies. The Examiner in Wands asserted that production of the required antibodies would have allegedly required undue experimentation. Id.

The Federal Circuit in Wands reversed, explaining that even though screening for hybridomas was labor-intensive with a number of steps (e.g., immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells, cloning the hybridoma, screening the resulting antibodies, etc.), all the methods needed to practice

the invention were well known, and "the amount of effort needed to obtain" the antibodies was not excessive so as to be undue. Id. at 1407.

The preparation of solvates of a given organic molecule is substantially easier, and experimentation more routine, than the production of antibodies considered by the Wands court. The process of preparing solvates requires significantly fewer steps, and demands much less experimentation than for the preparation of a monoclonal antibody considered by the Wands court.

By analogy therefore, if the Wands court concluded that the preparation of the monoclonal antibody under consideration was enabled despite the complex and lengthy process involved, the applicants believe the court would similarly find the production of the claimed solvates as being supported by an enabling disclosure, especially in view of the generally advanced level of skill in the art regarding the same.

The following Table provides a step-by-step comparison of some of the major steps involved in the production of a monoclonal antibody (as disclosed in In re Wands, 8 USPQ2d 1407) and the one step involved in making a solvate of the claims.

Table[1]

Step	Monoclonal Antibody	Solvate
1	immunize animal	expose the compound to water or solvent
2	remove the spleen from the immunized animal	
3	separate the lymphocytes from the other	

[1] There may be several other steps in the production of monoclonal antibodies not described in *Wands*, e.g., preparation of antigen, repeated immunization of animals, testing of animal serum for the presence and titer of the antibodies of choice, introduction of hybridoma cells into animals to induce liquid ascytes tumours, draining the ascytes tumors from the livings animals, purification of monoclonal antibodies from the ascytes fluids, etc.

	spleen cells	
4	Mix the lymphocytes with myeloma cells	
5	treat the mixture to cause fusion between the lymphocytes and the myeloma cells to make hybridomas that hopefully secrete the desired antibody	
6	separate the hybridoma cells from the unfused lymphocytes and myeloma cells by culturing in a medium in which only hybridoma cells survive	
7	culture single hybridoma cells (often 100 of different cells) in separate chambers	
8	assay the antibody secreted from each hybridoma culture to determine if it binds to the antigen	
Total Time	Months	About 1-2 days

As is clearly shown in the above Table, the process of production of a monoclonal antibody is more complex and time-consuming than the production of a hydrate or solvate. Given the findings by the Wands court, the applicants believe the court would also find the production of solvates of the claims to require less than undue experimentation.

While the complexity of the procedures for making monoclonal antibodies and solvate is highly disparate, the processes share the characteristic that the step(s) involved are well-known and routine.

Specifically, production of solvates, samples of an organic compound are exposed to water or various solvents. Once the solvates are formed, they can be readily analyzed by routine methods such as thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Karl Fischer titrimetry, X-ray diffractions (single crystal or powder), infrared spectroscopy (IR), polarized light microscopy, and hot stage

microscopy (see page 18, right column, Vippagunta et al. *Advanced Drug Delivery Reviews* 48 (2001) 3-26) or other routine techniques to detect and quantify the presence of solvate molecules in the sample. Exposure of the organic compounds to water and various solvents is conducted through simple and routine methods such as letting the samples sit open to air for set amounts of time, as well as slurrying and/or crystallizing the samples from water or solvent.

The applicants submit, with due respect to the Examiner, that placing a powder on a dish and letting it sit out on a humid day, as one means of making a hydrate, requires no undue experimentation. Other routine procedures for making and identifying hydrates and solvates are described, for example, on pages 202-209 of K.J. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: *Polymorphism in Pharmaceutical Solids*, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999.

While there may be many solvents and conditions to attempt, and number of species may be large, screening the products requires routine methods that are very well known in the art . In fact, there are numerous companies that routinely provide this screening service (usually combined with polymorph screens) and advertise how quickly and efficiently they can identify hydrates and solvates. Example companies offering these services include Wilmington PharmaTech (Wilmington, DE), Avantium Technologies (Amsterdam), and Aptuit (Greenwich, CT).

The applicants understand that the alleged unpredictability due to a low success rate of preparing monoclonal antibodies was rejected by the Wands court as a basis for

rejecting the Wands' claims for an alleged lack of enablement. The Wands court is understood to have found that all the methods needed to make the products used in the claimed method were well known and that the amount of effort was not undue despite what might have been a large amount of experimentation needed.

The Wands court is understood to have believed that even though the preparation of a monoclonal antibody involved unpredictable outcomes, the unpredictability has little weight against the fact that if an antibody could be made, it would almost certainly be made by the routine methods known in the art. By analogy, while the outcome of every feature and characteristic of a solvate of a given compound, such as the hygroscopicity, solvent/water content, type of hydrate/solvate (e.g., channel, isolated sites, etc.) may not be absolutely predictable, the production of the same however is well known and requires no more than routine experimentation.

Moreover, the success rate for making a solvate may not be 100%. However, like for antibodies, if a solvate or hydrate could be made, it would almost certainly be made by the routine methods for making solvates that are well-known in the art. Accordingly, any unpredictability associated with solvate formation that might exist is clearly outweighed by the fact that preparing and screening for solvates is routine and employs well-known methods.

With respect to the allegations of lack of sufficient direction or guidance and lack of working examples, Applicants respectfully note that the courts have held that what is well known in the art need not be taught in the application. Lindemann Maschinenfabrik v. American Hoist & Derrick Co., 221 USPQ 481, 489 (Fed. Cir. 1984). The courts have

further held that working examples are not necessary if the disclosure is such that one skilled in the art can practice the claimed invention. In re Borkowski, 164 USPQ 642 (C.C.P.A. 1970); Ex parte Nardi, 229 USPQ 79 (Pat. Off. Bd. App. 1986).

The applicants further submit that there is no requirement for the application to describe methods for making solvates and no need to show actual examples of the same because what is well known in the art need not be taught in the specification. One of ordinary skill in the art could make and use the claimed solvates without such exemplification. Preparation of solvates, as discussed at great length above, is well known in the art. The attached Guillory reference shows the well-known and routine nature of preparing hydrates and solvates. Thus, the present application need not describe any working examples or methods for making solvates, since what is well-known need not be taught and one of ordinary skill in the art would know how to make and use the claimed solvates.

Applicants further respectfully note that the courts have repeated held that a large amount of experimentation is not undue if it is merely routine. In re Wands, PPG Indus., Inc. v. Guardian Indus. Corp., 37 USPQ2d 1618, 1623 (Fed. Cir. 1996). As discussed above, making solvates is well-known and routine and, thus, preparing solvates of the presently claimed compounds would not require undue experimentation.

As the preparation of solvates involves the use of well known methods and would not require undue experimentation, and as patents are routinely issued with claims to solvates, the applicants respectfully submit that the presently claimed invention to

solvates are supported by an enabling disclosure and withdrawal of the Section 112, first paragraph "enablement", rejection of the claims based on the same is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required in this regard.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /B. J. Sadoff/
B. J. Sadoff
Reg. No. 36,663

BJS:
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100